Tetrahedron 66 (2010) 9902–9911

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chiral amines in the diastereoselective Mannich-related multicomponent synthesis of diarylmethylamines, 1,2-diarylethylamines, and β-arylethylamines

Caroline Haurena, Erwan LeGall *, Stéphane Sengmany, Thierry Martens

Électrochimie et Synthèse Organique, Institut de Chimie et des Matériaux Paris-Est, ICMPE, UMR 7182 CNRS—Université Paris-Est Créteil, 2-8 rue Henri Dunant, 94320 Thiais, France

ARTICLE INFO

Article history:
Received 23 September 2010
Received in revised form 19 October 2010
Accepted 21 October 2010
Available online 28 October 2010

Keywords:
Multicomponent reactions
Organozinc compounds
Diastereoselectivity
Cobalt
Zinc

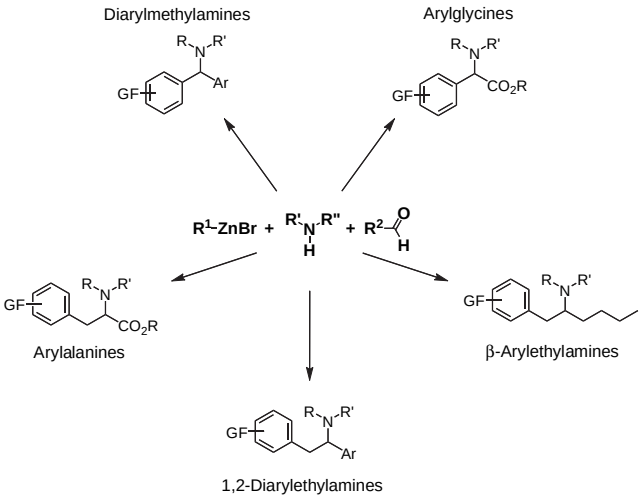
ABSTRACT

The multicomponent synthesis of diarylmethylamines, 1,2-diarylethylamines and β-arylethylamines has been undergone starting from aryl- or benzylzinc reagents, aldehydes, and primary or secondary chiral amines. Good to high diastereoselectivities have been obtained from both L-proline ester derivatives **1** and (±)-*trans*-1-allyl-2,5-dimethylpiperazine (**4**). The use of *R*-(+)-1-phenylethylamine (**7**) provides important diastereoisomeric excesses (~60%) in conjunction with very high chemical yields. This work constitutes a preliminary entry to the intended development of a more flexible reaction system, involving easily cleavable chiral amines.

1. Introduction

Multicomponent reactions (MCRs)[1,2] are known to constitute a powerful synthetic tool since they allow the straightforward formation of complex structures starting from simple substrates. Moreover, recent works have demonstrated that they represent very reliable processes for the preparation of important synthetic intermediates or natural products.[3] In this context, procedures related to the Mannich reaction[4] have been the subject of a tremendous development in the past few years. While thoroughly examined topics were regarding the development of unusual versions of the original reaction, in particular those employing organoboronic acids[5] or organometallic compounds[6,7] as nucleophiles equivalents, a particular emphasis was also placed on the development of diastereoselective MCRs involving (at least) one chiral substrate.[8]

As part of our work devoted to the development of MCRs employing organometallic reagents, we described recently a Mannich-type three-component reaction between amines, aldehydes and preformed or in situ-generated arylzinc or benzylzinc reagents (Barbier-like conditions). It was demonstrated that this reaction can provide a straightforward access to various molecular scaffolds like e.g., diarylmethylamines, 1,2-diarylethylamines, β-arylethylamines or α-amino esters.[9] To date, a rather important range of aldehydes, aryl halides and primary or secondary amines has already been evaluated in the process (Scheme 1). However, despite the common creation of an asymmetric carbon at the position α to the nitrogen, none of the starting compounds used were chiral.[10] Thus, the potential asymmetric induction provided by one of the reaction substrates was not assessed. Therefore, we found interesting to initiate a novel campaign of experiments focused on the



Scheme 1. Structural motifs accessible through a Mannich-type reaction between organozinc compounds, aldehydes and amines.

* Corresponding author. Tel.: +33 (0)149781135; fax: +33 (0)149781148; e-mail address: legall@glvt-cnrs.fr (E. LeGall).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.10.058

development of diastereoselective versions of the reaction. As a first disclosure of this current research interest, we report herein the possibility of operating from some primary or secondary chiral amines to obtain coupling products with satisfactory to very good diastereoisomeric excesses.

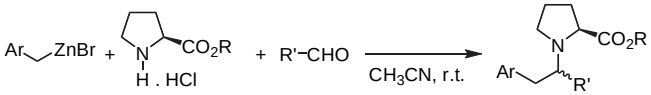
2. Results and discussion

In the first part of the study, we focused our attention on the reactivity of chiral cyclic secondary amines. Due to its wide commercial availability and its potential relevant integration into bioactive compounds,[11,12] L-proline derivatives **1** were first tested.

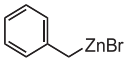
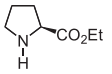
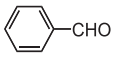
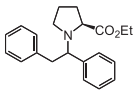
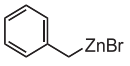
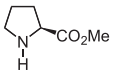
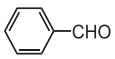
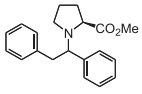
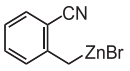
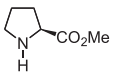
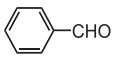
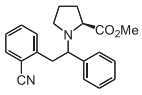
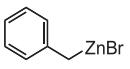
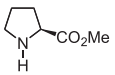
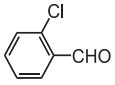
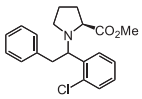
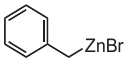
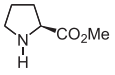
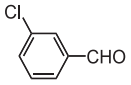
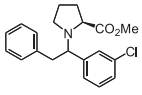
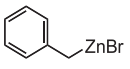
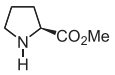
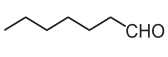
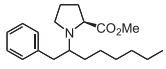
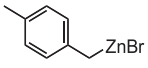
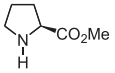
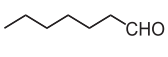
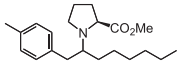
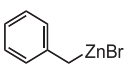
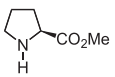
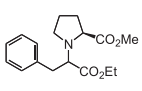
A preliminary experiment was realized starting from L-proline, benzylzinc bromide, and benzaldehyde, without protection of the carboxylic acid function. Indeed, it was assumed that after a probable deprotonation by the organozinc and under its carboxylate anion form, L-proline should be able to present interesting stereodifferentiating abilities and allow the formation of coupling products with important diastereoselectivities. In previous works, we had demonstrated that the presence of 2 equiv of the organozinc was necessary, even starting from non-functionalized secondary amines. Thus, in order to prevent the probable consumption of an additional equivalent of the organozinc reagent upon acid–base reaction with CO_2H, we decided to start with 3 equiv of this species. Unfortunately, these experiments resulted in failures and no coupling products were detected in the reaction medium, even after 24 h heating at 60 °C. We then decided to start from the corresponding ester derivatives. Thus, ethyl and methyl esters of L-proline[12] were engaged in three-component reactions with a range of aromatic or aliphatic aldehydes and organozinc compounds,[13] in situ-preformed from the corresponding benzyl bromides to avoid the formation of the *N*-benzylated product (resulting from the direct addition of the amine onto the starting benzyl bromide). Results are presented in Table 1.

It could be observed that the ethyl and the methyl ester function of proline provide comparable results, both in terms of diastereoselectivity and chemical yield (Table 1, entries 1 and 2). Then, we did not try to further expand the steric hindrance of the ester function and decided to undergo the following experiments starting from **1a**. The following results indicated that both a functionalized organozinc reagent and a functionalized aromatic aldehyde can be successfully used in the process (Table 1, entries 3–5). With 2- or 3-chlorobenzaldehyde as the starting aldehyde, we could notice that similar diastereoselectivities are obtained. However, the

Table 1
Multicomponent couplings starting from benzylzinc reagents, L-proline esters **1** and aldehydes[a]



1 **2a-h**

Entry	Benzylzinc bromide	Proline ester **1**	Aldehyde	Time (h)	Product		Diastereoisomeric excess[b] (de)	Yield[c] (%)
1				3		**2a**	54	45
2				3		**2b**	64	60
3				3		**2c**	72	51
4				3		**2d**	50	32
5				3		**2e**	54	42
6				2.5		**2f**	72	64
7				3		**2g**	76	65
8			EtO_2C–CHO	3		**2h**	20	23

[a] Reactions were conducted with 15 mL of acetonitrile, 7 mmol of the benzyl bromide, 2 mmol of the amine **1**, 2.4 mmol of the aldehyde, and 0.7 g (10.7 mmol) of zinc dust, pre-activated in the presence of TFA.
[b] Determined by ^{1}H NMR.
[c] Isolated yields.

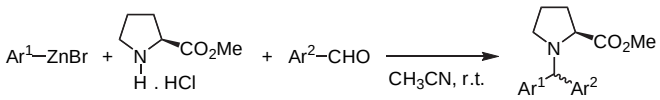
presence of the chloride at the *ortho* position provides a lower reaction yield (Table 1, entry 4). An aliphatic aldehyde is usable and provides coupling products in reasonable yields and diastereoisomeric excess (Table 1, entries 5 and 6). However, with ethyl glyoxylate as the carbonyl derivative, worse results are observed (Table 1, entry 8). A possible reason to this failure should rely in an unfavorable effect of both ester functions. Unfortunately, we were not able to interpret these observations on the basis of a reaction mechanism proposal.

We then investigated the outcome of the reactions involving aromatic organozinc reagents. Some preliminary experiments had revealed that their couplings with amines and aldehydes were more efficient when this reagent is used in the absence of zinc powder. Consequently, the organozinc reagent was preformed and transferred into the reaction flask containing the other reaction substrates, then allowed to react overnight at room temperature. Results are reported in Table 2.

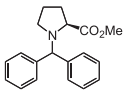
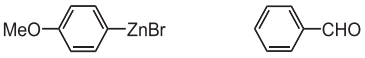
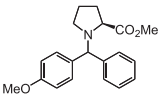
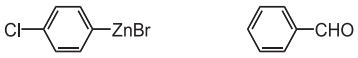
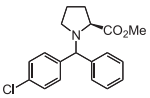
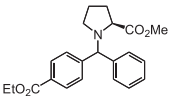
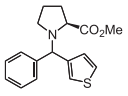
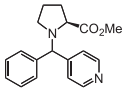
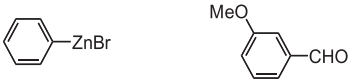
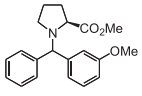
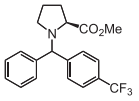
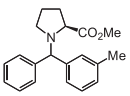
In all experiments, moderate to excellent diastereoselectivities were observed, with diastereoisomeric excesses ranging from 46% (Table 2, entry 4) to>90% (Table 2, entries 7 and 9). While the yields proved to be generally comparable to those observed with benzylzinc bromides, the reaction of aromatic organozinc reagents required longer reaction times (~24 h) than the reaction of benzylic organozinc reagents (~3 h). This result is not surprising since the increased reactivity of benzylzinc reagents in this multicomponent procedure had already been reported elsewhere.[9c]

In a following set of experiments, we envisaged assessing the reactivity of (±)-*trans*-1-allyl-2,5-dimethylpiperazine (*rac*-**4**) in the three-component coupling with benzylzinc bromide and benzaldehyde. This choice was motivated by the presence of this nitrogen-containing motif in the analgesic diarylmethylamines SNC-80[14] and BW373U86,[15] which are highly selective non-peptidic agonists of the δ-opioid receptor.[16] Preliminary experiments had indicated that the reaction was more difficult to carry out than expected. Indeed, it

Table 2
Multicomponent couplings starting from arylzinc reagents, L-proline methyl ester (**1a**), and aromatic aldehydes[a]

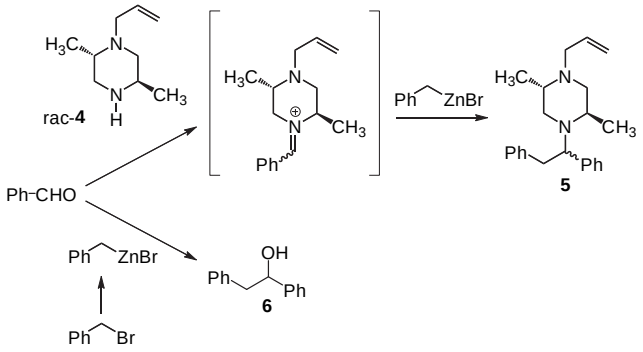


1a **3a-j**

Entry	Arylzinc bromide	Aldehyde	Time (h)	Product		Diastereoisomeric excess (de)[b]	Yield[c] (%)
1			21		**3a**	—	41
2			15		**3b**	74	36
3			20		**3c**	70	33
4			15		**3d**	46	41
5			20		**3f**	80	52
6			20		**3g**	78	23
7			22		**3h**	>90	61
8			20		**3i**	72	47
9			20		**3j**	>90	70

[a] Reactions were conducted with 40 mL of acetonitrile, 15 mmol of the aryl bromide, 0.83 g (5 mmol) of proline methyl ester hydrochloride, 5 mmol of the aldehyde, 0.66 g (3 mmol) of cobalt bromide, and 6 g (92 mmol) of zinc dust, pre-activated in the presence of methanesulfonic acid.
[b] Determined by ^{1}H NMR.
[c] Isolated yields.

was observed the concomitant formation of the three-component coupling product and the alcohol **6** resulting from the addition of the organozinc onto benzaldehyde (Scheme 2).



Scheme 2. Concurrent reaction pathways.

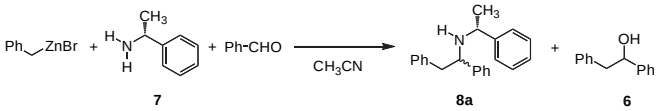
This effect might be the consequence of a limited nucleophilicity of the amine, thus indirectly favoring such direct organometallic addition rather than the formation of a formal iminium and it's trapping by the organozinc reagent. Consequently, we tried to explore some experimental adaptations devoted to the optimization of the reaction conditions. Main results are highlighted in Table 3.

Unfortunately, these experiments did not produce a satisfactory improvement of the three-component coupling. Indeed, similar limited yields were obtained, regardless of the reaction temperature (Table 3, entries 1 and 2), the mode of the organozinc compound formation (Table 3, entry 3) or the experimental technique, which was applied for the addition (Table 3, entry 4). However, we were satisfied to notice the very interesting excesses, which were observed in all cases, thus revealing the excellent stereo-differentiating abilities of the piperazine derivative in the three-component reaction. In addition, since the conversion of the starting amine was not quantitative at room temperature, the results reported in entry 4 should be prone to a sensible improvement, for instance by working at a slightly higher temperature.

of two closely related benzyl C–N bonds in most of the formed compounds, these methods should be difficultly applicable here.

Some preliminary experiments were realized though and indicated, as reported above with the amine **4**, that the formation of the alcohol **6** could constitute a significant limitation of the process. We then screened a set of reaction parameters and mainly chose to place a particular focus on the reaction temperature modulation. Main results are reported in Table 4.

Table 4
Multicomponent coupling starting from benzylzinc bromide, *R*-(+)-1-phenylethylamine (**7**), and benzaldehyde: optimization of the reaction conditions[a]



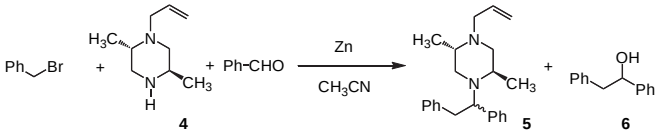
Entry	Temperature (°C)	Time (h)	**8a**/**6** ratio	Diastereoisomeric excess (de)[b]	Yield[c] (%)
1	0	2	82:18	60	62
2	10	1.5	90:10	72	82
3	25	1	72:25	50	56
4	60	1	50:50	40	53

[a] Reactions were conducted with 15 mL of acetonitrile, 0.85 g (5 mmol) of benzyl bromide, 0.25 g (2 mmol) of the benzylamine **7**, 0.25 g (2.4 mmol) of benzaldehyde, and 0.5 g (7.6 mmol) of zinc dust, pre-activated in the presence of TFA.
[b] Determined by ^{1}H NMR.
[c] Isolated yields of **8a**.

Very reliable reactions conditions, both in terms of chemical yield and diastereoselectivity, could be obtained by working at 10 °C (Table 4, entry 2), whereas other experiments suffered from a lack of diastereoselectivity (Table 4, entry 4) or worse reaction yields (Table 4, entries 1, 3, and 4). Thus, with these optimized conditions in hand, we decided to proceed further and chose to examine the reaction of *R*-(+)-1-phenylethylamine (**7**) with some benzylzinc reagents and aldehydes. Results are reported in Table 5.

These results confirmed those obtained with proline derivatives, particularly by demonstrating that a range of aromatic aldehydes are usable in the reaction. Interesting diastereoisomeric excesses, ranging from 50 to 72%, were obtained in all cases. However, as

Table 3
Multicomponent coupling starting from benzylzinc bromide, (±)-*trans*-1-allyl-2,5-dimethylpiperazine (**4**), and benzaldehyde[a]



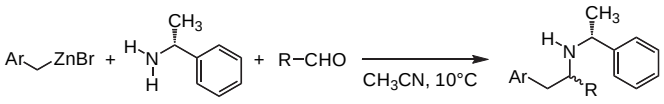
Entry	Phenylzinc bromide	Temperature (°C)	Time (h)	**5**/**6** ratio	Diastereoisomeric excess (de)[b]	Yield[c] (%)
1	Preformed	25	3	57:43	74	36
2	Preformed	10	15	68:32	80	34
3	In situ-generated	25	5	51:49	78	29
4	Preformed, dropwise addition	25	3	82:18	80	23[d]

[a] Reactions were conducted with 15 mL of acetonitrile, 0.85 g (5 mmol) of benzyl bromide, 0.31 g (2 mmol) of the piperazine **4**, 0.25 g (2.4 mmol) of benzaldehyde, and 0.5 g (7.6 mmol) of zinc dust, pre-activated in the presence of TFA.
[b] Determined by ^{1}H NMR.
[c] Isolated yields of **5**.
[d] The conversion of the starting amine was only partial.

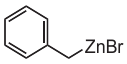
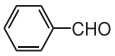
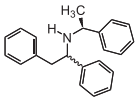
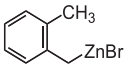
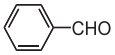
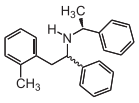
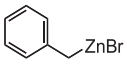
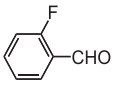
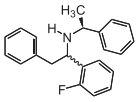
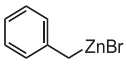
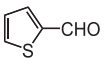
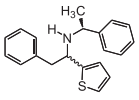
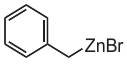
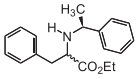
In a following part of the study, we focused our attention to the examination of reactions involving primary chiral amines. To this end, *R*-(+)-1-phenylethylamine (**7**) was chosen as the model substrate. Indeed, this amine does not only constitute one of the most reliable chiral inductors, both in terms of price and stereo-differentiating abilities,[17] it also generally provides the further opportunity of cleaving the *N*-benzyl bond either by e.g., hydrogenolysis[18] or nucleophilic substitution by iodide.[19] Nevertheless, due to the presence mentioned above (Table 1, entry 8), ethyl glyoxylate conducted to a lower reaction yield (Table 5, entry 5).

With the final aim of increasing the diastereoselectivity of the reaction, we tried to use a more bulky primary amine related to *R*-(+)-1-phenylethylamine (**7**). To this end, it was chosen to replace the phenyl by a naphtyl group. It can be noted that a strategy based on the use of *ortho*-naphtol to interact with an imine function and provide improved diastereoselectivities was employed by Alfonsov

Table 5
Multicomponent couplings starting from benzylzinc reagents, *R*-(+)-1-phenylethylamine (**7**) and aldehydes[a]



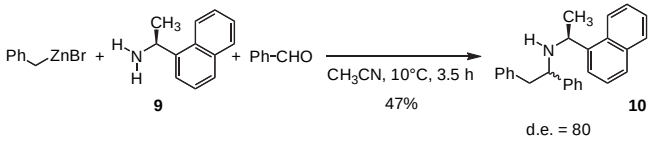
7 **8a-e**

Entry	Benzylzinc bromide	Aldehyde	Time (h)	Product		Diastereoisomeric excess (de)[b]	Yield (%)[c]
1			1.5		**8a**	72	82
2			2		**8b**	54	93
3			0.5		**8c**	60	84
4			0.5		**8d**	64	86
5		EtO_2C–CHO	2		**8e**	50	30

[a] Reactions were conducted with 15 mL of acetonitrile, 5 mmol of the benzyl bromide, 0.25 g (2 mmol) of the benzylamine **7**, 2.4 mmol of the aldehyde, and 0.5 g (7.6 mmol) of zinc dust, pre-activated in the presence of TFA.
[b] Determined by ^{1}H NMR.
[c] Isolated yields.

and co-workers in the synthesis of α-aminophosphonic acids.[20] However, this strategy might not be applicable here due to the ease of deprotonation of phenol derivatives and the probable inefficiency of phenolates in the process.

Thus, (*S*)-1-(naphthalen-1-yl)ethylamine (**9**) was allowed to react with benzylzinc bromide and benzaldehyde, providing the three-component coupling product in 47% yield and 80% de (Scheme 3).



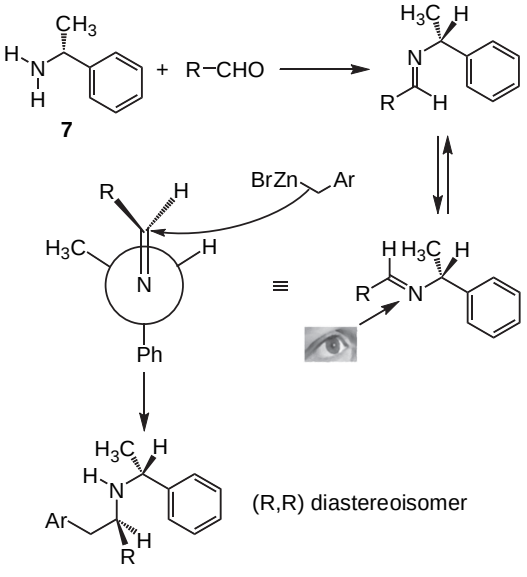
9 **10**

Scheme 3. Effect of the use of a more bulky aromatic group.

In spite of a notable decrease of the chemical yield, this experiment revealed that a more important steric discrimination between the methyl and the aryl group should result in a notable improvement of the diastereoselectivities. Consequently, this strategy might be extended to a larger range of α-methyl benzylamine derivatives, which may ideally both supply steric hindrance and deprotection opportunities by smooth and selective cleavage of the proper benzylic C–N bond. Ideally, the phenyl should bear one or more substituents, which could additionally provide activation of the C–N bond, in regard with the ease of deprotection. The search for such a reliable chiral auxiliary is currently in progress.[21]

While the assignment of the configurations of the asymmetric carbons could neither be done by conventional NMR methods nor crystallization and subsequent X-ray analysis, a predictive model close to that of Yamamoto[22] should be used to imagine the nature of the major diastereoisomer arising from primary chiral amines (Scheme 4).

In this case, we assume that the formation of the (*R*,*R*) diastereoisomer might be prevalent. However, only a selective debenzylation giving rise to the formation of a known enantiomer or a chemical correlation by the unambiguous preparation of one diastereoisomer should corroborate this hypothesis.



Scheme 4. Prediction of the major diastereoisomer.

3. Conclusion

In conclusion, this work shows that a range of chiral amines should be usable in the diastereoselective Mannich-related multicomponent synthesis of some model diarylmethylamines, 1,2-diarylethylamines, and β-arylethylamines, providing coupling products in generally good yields and diastereoisomeric excesses. While in this work, only harshly- or non-cleavable amines were used, it would be highly valuable to employ easily convertible chiral amines in the process, thus providing an access to enantioenriched primary or secondary amines after subsequent deprotection. Consequently, the design of a cleavable chiral amine, able to provide high yields and diastereoisomeric excesses of coupling products, would be highly desirable. The work presented herein thus constitutes a first entry to the conception of a more flexible reaction system, which will be the purpose of a further study.

4. Experimental

4.1. General

Solvents and reagents were purchased from commercial suppliers and used without further purification. All reactions were monitored by gas chromatography (GC) using a Varian 3400 chromatograph fitted with an SGE BP1 capillary column (l=5 m, Ø=0.32 mm, df=0.4 μm). Infrared spectra were recorded in ATR mode on a Bruker TENSOR 27 spectrometer and treated via OPUS software. NMR spectra were recorded in $CDCl_3$ (compounds **3a**–**j**) or CD_3OD (compounds **2a**–**h**, **5**, **8a**–**e**, **10**) at 400 MHz (^{1}H), 100 MHz (^{13}C), and 376 MHz (^{19}F) on a Bruker Avance II 400 spectrometer. Chemical shifts (δ) of the major diastereoisomer are reported in parts per million (ppm) relative to the residual solvent signal. Coupling constant values (J) are given in hertz (Hz) and refer to apparent multiplicities, indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were recorded in ESI^+ mode on a Trace 200 chromatograph fitted with a CPSIL5CB/MS capillary column (l=25 m, Ø=0.25 mm, df=0.12 μm). High Resolution Mass Spectrometry (HRMS) were performed by the Mass Spectrometry service of the ICSN (Institut de Chimie des Substances Naturelles), Gif-sur-Yvette, France. Compounds, which have been previously described in the literature are linked to the corresponding bibliographic references whereas compounds labeled by asterisk (*) are, to the best of our knowledge, new compounds.

4.2. Typical procedure for the coupling of a benzyl bromide with (*S*)-methyl pyrrolidine-2-carboxylate (1a) or (*S*)-ethyl pyrrolidine-2-carboxylate (1b) and an aldehyde (Table 1, preparation of compounds 2a–h)

A dried 25 mL round-bottomed flask was flushed with argon and charged with acetonitrile (15 mL). Zinc dust (0.7 g, 10.7 mmol) and trifluoroacetic acid (0.04 mL) were added under vigorous stirring. After 5 min, the benzyl bromide (7 mmol) was added and the mixture stirred for 10 min. The amine (2 mmol) and the aldehyde (2.4 mmol) were added and the resulting solution was stirred for 2.5–3 h at room temperature. The reaction was quenched with a saturated ammonium chloride solution (50 mL) and the organic products extracted with dichloromethane (2×100 mL). After removal of the solvent, a chromatographic purification on a silica gel column using a pentane/dichloromethane/triethylamine mixture as the eluent (88/10/2) afforded the pure product.

4.3. Typical procedure for the coupling of an aryl bromide with (*S*)-methyl pyrrolidine-2-carboxylate and an aldehyde (Table 2, preparation of compounds 3a–j)

A dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (40 mL). Cobalt bromide (0.7 g, 3 mmol), zinc bromide (0.66 g, 3 mmol), zinc dust (6 g, 92 mmol), and methanesulfonic acid (0.02 mL) were successively added under vigorous stirring. After 5 min, aryl bromide (15 mmol) was added and the mixture was stirred for 30 min. After decantation, the clear arylzinc solution was transferred dropwise using a syringe to a mixture of the amine (5 mmol) and the aldehyde (5 mmol) in ethylene glycol dimethyl ether (5 mL). The solution was stirred at room temperature overnight. The reaction was quenched with a saturated sodium carbonate solution (50 mL) and the organic solution extracted with dichloromethane (2×100 mL). After removal of the solvent, a chromatographic purification on a silica gel column using a pentane/diethyl ether mixture as the eluent afforded the pure product.

4.4. Typical procedure for the coupling of benzyl bromide with (±)-*trans*-1-allyl-2,5-dimethylpiperazine and benzaldehyde (Table 3, preparation of compound 5)

A dried 25 mL round-bottomed flask was flushed with argon and charged with acetonitrile (15 mL). Zinc dust (0.5 g, 7.6 mmol) and trifluoroacetic acid (0.03 mL) were added under vigorous stirring. After 5 min, benzyl bromide (0.85 g, 5 mmol) was added and the mixture was stirred for 10 min. If required, the mixture was cooled down and (±)-*trans*-1-allyl-2,5-dimethylpiperazine (0.31 g, 2 mmol) and benzaldehyde (0.25 g, 2.4 mmol) were added. The resulting solution was stirred for 3–15 h. The reaction was quenched with a saturated ammonium chloride solution (50 mL) and the organic products extracted with dichloromethane (2100 mL). After removal of the solvent, a chromatographic purification on a silica gel column using a pentane/dichloromethane/triethylamine mixture as the eluent (88/10/2) afforded the pure product.

4.5. Typical procedure for the coupling of a benzyl bromide with (*R*)-1-phenylethylamine (7) or (*S*)-1-(naphthalen-1-yl) ethylamine (9) and an aldehyde (preparation of compounds 8a–e and 10)

A dried 25 mL round-bottomed flask was flushed with argon and charged with acetonitrile (15 mL). Zinc dust (0.5 g, 7.6 mmol) and trifluoroacetic acid (0.03 mL) were added under vigorous stirring. After 5 min, the benzyl bromide (5 mmol) was added and the solution stirred for 10 min. The mixture was then cooled to 10 °C and the amine (2 mmol) and the aldehyde (2.4 mmol) were added. The resulting solution was stirred for 0.5–3 h at 10 °C. The reaction was quenched with a saturated ammonium chloride solution (50 mL) and the organic products extracted with dichloromethane (2×100 mL). After removal of the solvent, a chromatographic purification on a silica gel column using a pentane/dichloromethane/triethylamine mixture as the eluent (93/5/2) afforded the pure product.

4.6. Characterization data

4.6.1. (2S)-Ethyl 1-(1,2-diphenylethyl)pyrrolidine-2-carboxylate (**2a**).* Pale yellow oil FT-IR (neat, cm^{-1}): ν 3062, 3028, 2975, 1727, 1602, 1495, 1453, 1369, 1269, 1174, 1080, 1028, 747, 698. ^{1}H NMR: δ 7.16–7.14 (m, 1H), 7.13 (d, J=4.4 Hz, 2H), 7.12–7.10 (m, 2H), 7.06–7.04 (m, 2H), 7.04–7.00 (m, 1H), 6.85–6.81 (m, 2H), 3.75 (dd, J=10.8, 4.0 Hz, 1H), 3.53 (dd, J=6.1, 3.5 Hz, 1H), 3.50 (q, J=7.0 Hz, 2H), 3.37 (dd, J=13.2, 4.1 Hz, 1H), 3.30–3.25 (m, 1H), 2.91 (dd, J=12.7, 10.6 Hz, 1H), 2.71–2.64 (m, 1H), 2.18–2.01 (m, 2H), 1.97–1.76 (m, 2H), 1.19 (t, J=7.0 Hz, 3H). ^{13}C NMR:

δ 177.0, 142.6, 140.1, 130.5, 130.3, 128.9, 128.4, 126.8, 72.8, 65.1, 61.5, 53.8, 51.2, 42.7, 31.1, 24.7, 14.5. MS, *m/z* (relative intensity): 250 ($[M-CO_2C_2H_5]^+$, 8), 232 ($[M-C_7H_7]^+$, 100), 204 (60), 181 ($[C_{14}H_{13}]^+$, 8), 135 (15), 91 ($[C_7H_7]^+$, 6), 70 (39). HRMS calcd for $C_{21}H_{25}NO_2$ $[M+H]^+$: 324.1964, found: 324.1976.

4.6.2. (2S)-Methyl 1-(1,2-diphenylethyl)pyrrolidine-2-carboxylate (**2b**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3062, 3025, 2974, 1729, 1600, 1495, 1453, 1171, 1079, 747, 698. ^1H NMR: δ 7.15–7.09 (m, 5H), 7.06–7.01(m, 3H), 6.85–6.81 (m, 2H), 3.72 (dd, *J*=10.9, 4.4 Hz, 1H), 3.53 (dd, *J*=9.8, 3.6, 1H), 3.43 (s, 3H), 3.36 (dd, *J*=12.8, 4.1 Hz, 1H), 2.95–2.88 (m, 1H), 2.71–2.63 (m, 1H), 2.14–2.07 (m, 1H), 1.99–1.77 (m, 4H). ^{13}C NMR: δ 177.3, 142.3, 140.2, 130.5, 130.3, 129.0, 128.9, 128.4, 126.8, 72.8, 65.0, 53.7, 52.0, 42.9, 31.1, 24.7. MS, *m/z* (relative intensity): 250 ($[M-CO_2CH_3]^+$, 5), 218 ($[M-C_7H_7]^+$, 100), 181 ($[C_{14}H_{13}]^+$, 7), 121 (92), 91 ($[C_7H_7]^+$, 10), 70 (7). HRMS calcd for $C_{20}H_{23}NO_2$ $[M+H]^+$: 310.1807, found: 310.1804.

4.6.3. (2S)-Methyl 1-(2-(2-cyanophenyl)-1-phenylethyl)pyrrolidine-2-carboxylate (**2c**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3062, 3029, 2949, 2843, 2223, 1731, 1599, 1486, 1451, 1434, 1273, 1195, 1167, 1086, 759, 701. ^1H NMR: δ 7.54–7.50 (m, 1H), 7.30–7.26 (m, 1H), 7.23–7.19 (m, 1H), 7.16–7.14 (m, 1H), 7.16–7.12 (m, 1H), 7.15–7.10 (m, 2H), 6.89 (d, *J*=7.6 Hz, 1H), 3.90 (dd, *J*=11.6, 3.8 Hz, 1H), 3.62 (dd, *J*=13.0, 4.8 Hz, 1H), 3.49 (dd, *J*=9.6, 3.7 Hz, 1H), 3.41 (s, 3H), 3.10 (dd, *J*=12.9, 11.2 Hz, 1H), 2.84–2.75 (m, 2H), 2.20–2.08 (m, 1H), 2.00–1.87 (m, 2H), 1.86–1.77 (m, 1H). ^{13}C NMR: δ 177.4, 144.0, 141.4, 133.6, 133.5, 132.2, 130.2, 129.1, 128.8, 127.9, 119.3, 114.0, 71.6, 65.3, 53.7, 52.1, 41.3, 31.2, 24.8. MS, *m/z* (relative intensity): 327 (7), 281 (23), 275 ($[M-CO_2CH_3]^+$, 10), 253 (18), 225 (7), 218 ($[M-C_8H_6N]^+$, 100), 207 (76), 191 (16), 179 (9), 121 (43), 91 (8), 70 (6). HRMS calcd for $C_{21}H_{22}N_2O_2$ $[M+H]^+$: 335.1760, found: 335.1758.

4.6.4. (2S)-Methyl 1-(1-(2-chlorophenyl)-2-phenylethyl)pyrrolidine-2-carboxylate (**2d**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3062, 3028, 2949, 2843, 1732, 1495, 1471, 1435, 1354, 1262, 1194, 1167, 1051, 1034, 756, 699. ^1H NMR: δ 7.63–7.58 (m, 2H), 7.14–7.10 (m, 2H), 7.06–7.03 (m, 3H), 6.91–6.87 (m, 2H), 4.55 (dd, *J*=10.7, 4.5 Hz, 1H), 3.57–3.51 (m, 2H), 3.42 (s, 3H), 3.41–3.35 (m, 1H), 2.92 (dd, *J*=13.0, 10.8 Hz, 1H) 2.72–2.74 (m, 1H), 2.18–2.07 (m, 1H), 2.00–1.78 (m, 4H). ^{13}C NMR: δ 177.2, 139.9, 139.1, 135.9, 131.7, 130.5 (two peaks), 130.1, 129.5, 129.4, 128.8, 127.7, 127.0, 66.1, 64.9, 53.6, 52.0, 42.4, 31.2, 24.8. MS, *m/z* (relative intensity): 284 ($[M-CO_2CH_3]^+$, 7), 252 ($[M-C_7H_7]^+$, 100), 215 ($[M-C_6H_{10}NO_2]^+$, 5), 157 (13), 155 (39). HRMS calcd for $C_{20}H_{22}ClNO_2$ $[M+H]^+$: 344.1417, found: 344.1424.

4.6.5. (2S)-Methyl 1-(1-(3-chlorophenyl)-2-phenylethyl)pyrrolidine-2-carboxylate (**2e**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3062, 3027, 2949, 2841, 1731, 1595, 1573, 1474, 1454, 1194, 1166, 1077, 787, 750, 698. ^1H NMR: δ 7.17 (s, 1H), 7.15–7.13 (m, 1H), 7.13–7.12 (m, 1H), 7.11–7.07 (m, 2H), 7.07–7.04 (m, 1H), 6.99–6.95 (m, 1H), 6.85 (d, *J*=7.5 Hz, 2H), 3.75 (dd, *J*=11.5, 4.9 Hz, 1H), 3.51 (dd, *J*=9.6, 3.3 Hz, 1H), 3.48 (s, 3H), 3.37 (dd, *J*=13.4, 4.7 Hz, 1H), 3.29–3.22 (m, 1H), 2.90–2.82 (m, 1H), 2.68 (q, *J*=7.4 Hz, 1H), 2.16–2.05 (m, 1H), 1.93–1.95 (m, 2H), 1.85–1.78 (m, 1H). ^{13}C NMR: δ 177.2, 145.2, 139.6, 134.9, 130.5, 130.3, 130.1, 129.0, 128.7, 128.4, 127.1, 72.2, 65.2, 53.5, 52.0, 42.7, 31.1, 24.0. MS, *m/z* (relative intensity): 284 ($[M-CO_2Me]^+$, 8), 252 ($[M-C_7H_7]^+$, 100), 179 (9), 155 (41), 130 (5). HRMS calcd for $C_{20}H_{22}ClNO_2$ $[M+H]^+$: 344.1417, found: 344.1421.

4.6.6. (2S)-Methyl 1-(1-phenyloctan-2-yl)pyrrolidine-2-carboxylate (**2f**).* Pale yellow oil. FT-IR (neat, cm^{-1}): ν 2957, 2927, 2855, 1732, 1704, 1495, 1455, 1435, 1194, 1165, 1102, 744, 699. ^1H NMR: δ 7.16–7.13 (m, 1H), 7.07–7.04 (m, 4H), 3.58 (s, 3H), 3.46 (dd, *J*=8.2, 4.3 Hz,1H), 2.91–2.85 (m,1H), 2.84–2.81 (m,1H), 2.80–2.76 (m,1H), 2.70–2.62 (m, 1H), 2.42–2.33 (m, 1H), 1.85–1.77 (m, 2H), 1.76–1.68 (m, 2H), 1.30–1.24 (m, 3H), 1.18–1.11 (m, 2H), 1.11–1.02 (m, 5H), 0.75 (t, *J*=7.3 Hz, 3H). ^{13}C NMR: δ 177.6, 142.0, 130.3, 129.4, 126.9, 63.7, 62.6, 52.2, 47.1, 36.7, 33.3, 33.0, 30.6, 30.2, 27.1, 25.1, 23.7, 14.5. MS, *m/z* (relative intensity): 226 ($[M-C_7H_7]^+$, 100), 166 (24), 70 (8). HRMS calcd for $C_{20}H_{31}NO_2$ $[M+H]^+$: 318.2433, found: 318.2429.

4.6.7. (2S)-Methyl 1-(1-(p-tolyl)octan-2-yl)pyrrolidine-2-carboxylate (**2g**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3047, 2926, 2855, 1733, 1704, 1515, 1457, 1436, 1276, 1194, 1165, 803, 758, 724. ^1H NMR: δ 7.10–7.02 (m, 4H), 3.68 (s, 3H), 3.56 (dd, *J*=8.2, 4.2 Hz, 1H), 3.00–2.94 (m, 1H), 2.92–2.83 (m, 2H), 2.80–2.72 (m, 1H), 2.43 (dd, *J*=12.3, 8.2 Hz, 1H), 2.30 (s, 3H), 2.02–1.95 (m, 1H), 1.94–1.86 (m, 2H), 1.85–1.78 (m, 1H), 1.40–1.35 (m, 3H), 1.26–1.22 (m, 2H), 1.21–1.14 (m, 5H), 0.86 (t, *J*=6.9 Hz, 3H). ^{13}C NMR: δ 177.3, 138.8, 136.4, 130.2, 130.0, 63.6, 62.5, 52.2, 47.1, 36.3, 33.3, 32.9, 30.5, 30.2, 27.1, 25.0, 23.7, 21.1, 14.4. MS, *m/z* (relative intensity): 226 ($[M-C_8H_9]^+$, 100), 166 (46), 70 (13). HRMS calcd for $C_{21}H_{33}NO_2$ $[M+H]^+$: 332.2590, found: 332.2581.

4.6.8. (2S)-Methyl 1-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxylate (**2h**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 2974, 2926, 2851, 1726, 1488, 1437, 1310, 1165, 1004, 749, 700. ^1H NMR: δ 7.28–7.23 (m, 2H), 7.22–7.17 (m, 2H), 7.20–7.17 (m, 1H), 3.98 (q, *J*=7.3 Hz, 2H), 3.83 (dd, *J*=9.1, 6.7 Hz, 1H), 3.61 (s, 3H), 3.19–3.03 (m, 1H), 3.09–3.03 (m, 1H), 3.03–2.98 (m, 1H), 2.83–2.76 (m, 2H), 2.20–2.06 (m, 1H), 1.95–1.89 (m, 1H), 1.87–1.80 (m, 2H), 1.14 (t, *J*=8.7 Hz, 3H). ^{13}C NMR: δ 176.2, 173.3, 139.5, 130.2, 129.3, 127.4, 65.8, 63.9, 61.4, 52.4, 52.3, 37.8, 30.4, 24.7, 14.6. MS, *m/z* (relative intensity): 246 ($[M-CO_2Me]^+$, 41), 232 ($[M-CO_2Et]^+$, 95), 214 ($[M-C_7H_7]^+$, 100), 186 (24), 172 (40), 158 (6), 135 (6), 103 (5), 70 (10). HRMS calcd for $C_{17}H_{23}NO_4$ $[M+H]^+$: 306.1705, found: 306.1708.

4.6.9. (S)-Methyl 1-benzhydrylpyrrolidine-2-carboxylate (**3a**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 2949, 1731, 1659, 1450, 1276, 1196, 1168, 698. ^1H NMR: δ 7.55 (t, *J*=7.1 Hz, 4H), 7.33 (q, *J*=7.2 Hz, 4H), 7.24 (q, *J*=6.9 Hz, 2H), 4.98 (s, 1H), 3.58 (dd, *J*=9.0, 3.0 Hz, 1H), 3.51 (s, 3H), 3.11 (q, *J*=4.8 Hz, 1H), 2.70 (q, *J*=8.8 Hz, 1H), 2.23–2.14 (m, 1H), 2.05–1.93 (m, 3H). ^{13}C NMR: δ 175.2, 143.5, 143.1, 128.4, 128.3, 128.1, 128.0, 127.1, 127.1, 72.8, 63.3, 52.1, 51.1, 30.2, 23.7. MS, *m/z* (relative intensity): 295 ($[M]^+$, 10), 237 (5), 236 ($[M-CO_2Me]^+$, 32), 168 (15), 167 ([M−Pro-OMe]$^+$, 100), 166 (8), 165 (21), 152 (10). HRMS calcd for $C_{19}H_{21}NO_2$ $[M+H]^+$: 296.1651, found: 296.1649.

4.6.10. (2S)-Methyl 1-((4-methoxyphenyl)(phenyl)methyl) pyrrolidine-2-carboxylate (**3b**).* Pale yellow oil. FT-IR (neat, cm^{-1}): ν 2950, 1731, 1609, 1509, 1453, 1245, 1169, 1030, 700. ^1H NMR: δ 7.34 (d, *J*=7.5 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H), 7.16 (t, *J*=7.5 Hz, 2H), 7.06 (q, *J*=7.2 Hz, 1H), 6.70 (d, *J*=8.3 Hz, 2H), 4.64 (s, 3H), 3.38–3.36 (m, 1H), 3.35 (s, 3H), 2.91–2.86 (m, 1H), 2.56–2.50 (m, 1H), 2.06–2.01 (m, 1H), 1.87–1.74 (m, 3H). ^{13}C NMR: δ 175.3, 158.6, 143.8, 135.3, 129.0, 128.2, 127.9, 126.9, 113.7, 71.9, 63.3, 55.2, 51.9, 51.1, 30.1, 23.6. MS, *m/z* (relative intensity): 325 ($[M]^+$, 9), 266 ($[M-CO_2Me]^+$, 11), 198 (15), 197 ([M−Pro-OMe]$^+$, 100), 182 (7), 166 (5), 165 (8). HRMS calcd for $C_{20}H_{23}NO_3$ $[M+H]^+$: 326.1756, found: 326.1759.

4.6.11. (2S)-Methyl 1-((4-chlorophenyl)(phenyl)methyl) pyrrolidine-2-carboxylate (**3c**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 2949, 1731, 1660, 1488, 1273, 1197, 1169, 1088, 698. ^1H NMR: δ 7.43 (t, *J*=8.5 Hz, 4H), 7.32–7.18 (m, 5H), 4.79 (s, 1H), 3.51–3.48 (m, 1H), 3.49 (s, 3H), 3.05–2.99 (m, 1H), 2.67–2.2.61 (m, 1H), 2.20–2.14 (m, 1H), 2.00–1.78 (m, 3H). ^{13}C NMR: δ 175.11, 142.93, 141.71, 132.68, 129.19, 128.58, 128.41, 127.90, 127.32, 71.98, 63.11, 52.08, 51.20, 30.18, 23.55. MS, *m/z* (relative intensity): 329 ($[M]^+$, 8), 294 ($[M-Cl]^+$, 8), 272 (14), 271 (9), 270 ($[M-CO_2Me]^+$, 42), 203 (34), 202 (15), 201

([M−Pro-OMe]$^+$, 100), 167 (5), 166 (37), 165 (38), 164 (5). HRMS calcd for $C_{19}H_{20}ClNO_2$ [M+H]$^+$: 330.1261, found: 330.1272.

4.6.12. (2S)-Methyl 1-(((4-ethoxycarbonyl)phenyl) (phenyl)methyl) pyrrolidine-2-carboxylate (**3d**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 2951, 1714, 1609, 1271, 1100, 1020, 710. ^{1}H NMR: δ 7.96 (t, J=6.1 Hz, 2H), 7.55 (t, J=6.1 Hz, 2H), 7.44–7.39 (m, 3H), 7.25–7.15 (m, 2H), 4.90 (s, 1H), 4.31 (q, J=6.9 Hz, 2H), 3.51–3.47 (m, 1H), 3.46 (s, 3H), 2.99–2.96 (m, 1H), 2.67–2.60 (m, 1H), 2.15–2.11 (m, 1H), 1.92–1.83 (m, 3H), 1.33 (t, J=6.9 Hz, 3H). ^{13}C NMR: δ 174.9, 166.3, 148.7, 142.6, 129.6, 128.5, 128.0, 128.0, 127.7, 127.3, 71.9, 62.9, 60.7, 52.1, 51.1, 30.0, 23.4, 14.3. MS, m/z (relative intensity): 367 ([M]$^+$, 7), 309 (11), 308 ([M−CO_2Me]$^+$, 57), 240 (18), 239 ([M−Pro-OMe]$^+$, 100), 167 (18), 166 (15), 165 (20). HRMS calcd for $C_{22}H_{25}NO_4$ [M+H]$^+$: 368.1862, found: 368.1880.

4.6.13. (2S)-Methyl 1-(phenyl(thiophen-3-yl)methyl)pyrrolidine-2-carboxylate (**3f**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 2948, 2842, 1730, 1651, 1452, 1434, 1275, 1196, 1158, 704. ^{1}H NMR: δ 7.48 (d, J=7.4 Hz, 2H), 7.32 (t, J=7.4 Hz, 2H), 7.25–7.17 (m, 2H), 7.12 (d, J=4.9 Hz, 1H), 4.87 (s, 1H), 3.53 (s, 3H), 3.46 (dd, J=9.4, 4.1 Hz, 1H), 3.08–3.04 (m, 1H), 2.56 (q, J=9.0 Hz, 1H), 2.16–2.09 (m, 1H), 1.99–1.79 (m, 3H). ^{13}C NMR: δ 175.2, 144.5, 142.3, 128.4, 128.0, 127.7, 127.2, 125.3, 122.2, 68.3, 63.4, 52.2, 51.3, 30.2, 23.6. MS, m/z (relative intensity): 301 ([M]$^+$, 19), 243 (6), 242 ([M−CO_2Me]$^+$, 33), 175 (6), 174 (12), 173 ([M−Pro-OMe]$^+$, 100), 172 (5), 171 (8), 129 (17). HRMS calcd for $C_{17}H_{19}NO_2S$ [M+H]$^+$: 302.1215, found: 302.1226.

4.6.14. (2S)-Methyl 1-(phenyl(pyridin-4-yl)methyl)pyrrolidine-2-carboxylate (**3g**).* Brown oil. FT-IR (neat, cm^{-1}): ν 3028, 2950, 1730, 1666, 1596, 1413, 1279, 1198, 1170, 700. ^{1}H NMR: δ 8.50 (d, J=5.9 Hz, 2H), 7.40 (d, J=5.9 Hz, 2H), 7.36 (d, J=7.3 Hz, 2H), 7.29 (t, J=7.2 Hz, 2H), 7.23 (t, J=7.2 Hz, 1H), 4.88 (s, 1H), 3.51 (s, 3H), 3.48–3.36 (m, 1H), 2.96–2.92 (m, 1H), 2.68 (q, J=8.2 Hz, 1H), 2.18–2.12 (m, 1H), 1.97–1.83 (m, 3H). ^{13}C NMR: δ 174.9, 152.3, 150.0, 140.9, 128.6, 128.2, 127.7, 122.8, 70.7, 62.7, 51.2, 51.0, 29.8, 23.4. MS, m/z (relative intensity): 296 ([M]$^+$, 6), 238 (10), 237 ([M−CO_2Me]$^+$, 63), 195 (5), 169 (14), 168 ([M−Pro-OMe]$^+$, 100), 167 (35). HRMS calcd for $C_{18}H_{20}N_2O_2$ [M+H]$^+$: 297.1603, found: 297.1594.

4.6.15. (2S)-Methyl 1-((3-methoxyphenyl)(phenyl)methyl)pyrrolidine-2-carboxylate (**3h**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 2949, 1731, 1597, 1487, 1451, 1434, 1279, 1257, 1159, 1041, 704. ^{1}H NMR: δ 7.34 (d, J=7.3 Hz, 2H), 7.15 (t, J=7.3 Hz, 2H), 7.12–7.05 (m, 2H), 6.96–6.91 (m, 2H), 6.61–6.58 (m, 2H), 4.65 (s, 1H), 3.64 (s, 3H), 3.39–3.34 (m, 4H), 2.93–2.87 (m, 1H), 2.55 (q, J=8.9 Hz, 1H), 2.05–2.00 (m, 1H), 1.86–1.68 (m, 3H). ^{13}C NMR: δ 175.4, 159.6, 145.2, 129.2, 128.3, 127.9, 127.1, 120.4, 113.5, 112.5, 72.7, 63.2, 55.1, 52.1, 51.1, 30.2, 23.6. MS, m/z (relative intensity): 325 ([M]$^+$, 17), 267 (9), 266 ([M−CO_2Me]$^+$, 42), 198 (17), 197 ([M−Pro-OMe]$^+$, 100), 182 (14), 181 (6), 179 (5), 169 (9), 166 (6), 165 (16), 154 (5), 153 (7). HRMS calcd for $C_{20}H_{23}NO_3$ [M+H]$^+$: 326.1756, found: 326.1764.

4.6.16. (2S)-Methyl 1-(phenyl(4-(trifluoromethyl)phenyl)methyl) pyrrolidine-2-carboxylate (**3i**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 2992, 1732, 1618, 1323, 1198, 1160, 1119, 1065, 700. ^{1}H NMR: δ 7.64 (d, J=8.1 Hz, 2H), 7.55 (d, J=8.1 Hz, 2H), 7.44 (d, J=7.5 Hz, 2H), 7.31 (t, J=7.5 Hz, 2H), 2.24 (t, J=7.4 Hz, 1H), 4.94 (s, 3H), 3.53 (dd, J=9.0, 2.7 Hz, 1H), 3.49 (s, 3H), 3.04–2.99 (m, 1H), 2.69 (q, J=8.4 Hz, 1H), 2.21–2.16 (m, 1H), 2.02–1.90 (m, 3H). ^{13}C NMR: δ (ppm): 175.1, 147.6, 141.9, 129.2 (q, J=32.0 Hz), 128.6, 128.2, 128.0, 127.5, 125.3 (q, J=3.0 Hz), 124.2 (q, J=270.0 Hz), 71.7, 63.0, 51.5, 51.2, 30.2, 23.4. ^{19}F NMR: δ −63.00. MS, m/z (relative intensity): 363 ([M]$^+$, 6), 344 (5), 305 (13), 304 ([M−CO_2Me]$^+$, 67), 236 (14), 235 ([M−Pro-OMe]$^+$, 100), 216 (5), 215 (16), 166 (12), 165 (12). HRMS calcd for $C_{20}H_{20}F_3NO_2$ [M+H]$^+$: 364.1524, found: 364.1517.

4.6.17. (2S)-Methyl 1-(phenyl(4-(m-tolyl)methyl))pyrrolidine-2-carboxylate (**3j**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 2949, 1731, 1659, 1279, 1197, 1160, 705. ^{1}H NMR: δ 7.49 (d, J=7.3 Hz, 2H), 7.32–7.29 (m, 4H), 7.23–7.16 (m, 2H), 7.02 (d, J=6.9 Hz, 1H), 4.77 (s, 1H), 3.53–3.49 (m, 1H), 3.50 (s, 3H), 3.07–3.02 (m, 1H), 2.67 (q, J=8.9 Hz, 1H), 2.34 (s, 3H), 2.21–2.13 (m, 1H), 2.02–1.90 (m, 3H). ^{13}C NMR: δ 175.3, 143.4, 143.2, 137.7, 128.7, 128.4, 128.2, 128.1, 127.4, 127.0, 125.1, 72.9, 63.4, 52.2, 51.1, 30.2, 23.6, 21.6. MS, m/z (relative intensity): 309 ([M]$^+$, 9), 251 (7), 250 ([M−CO_2Me]$^+$, 28), 182 (15), 181 ([M−Pro-OMe]$^+$, 100), 166 (20), 165 (18). HRMS calcd for $C_{20}H_{23}NO_2$ [M+H]$^+$: 310.1807, found: 310.1801.

4.6.18. (2S,5R)-1-Allyl-4-(1,2-diphenylethyl)-2,5-dimethylpiperazine (**5**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3061, 3023, 2971, 2926, 2818, 1493, 1450, 1375, 1338, 1176, 1151, 1070, 1055, 997, 915, 744, 726, 694. ^{1}H NMR: δ 7.39 (d, J=7.5 Hz, 2H), 7.26 (t, J=7.5 Hz, 2H), 7.21–7.17 (m, 1H), 7.17–7.15 (m, 2H), 7.15–7.13 (m, 2H), 7.08–7.05 (m, 1H), 5.96–5.84 (m, 1H), 5.29–5.25 (m, 1H), 5.25–5.20 (m, 1H), 4.44 (t, J=7.6 Hz, 1H), 3.51–3.44 (m, 1H), 3.19 (d, J=7.3 Hz, 2H), 3.00–2.94 (m, 1H), 2.93–2.88 (m, 1H), 2.88–2.84 (m, 1H), 2.66 (dd, J=11.5, 2.7 Hz, 1H), 2.36 (t, J=10.1 Hz, 1H), 2.26–2.18 (m, 1H), 2.11 (t, J=10.1 Hz, 1H), 1.27 (d, J=6.5 Hz, 3H), 1.02 (d, J=5.9 Hz, 3H). ^{13}C NMR: δ 141.6, 141.3, 134.2, 130.9, 130.2, 129.3, 128.9, 128.0, 126.8, 119.9, 64.0, 60.7, 57.5, 57.1, 53.5, 52.9, 30.8, 17.9, 16.9. MS, m/z (relative intensity): 243 (100), 228 (12), 201 (36), 91 ([C_7H_7]$^+$, 15). HRMS calcd for $C_{23}H_{30}N_2$ [M+H]$^+$: 335.2487, found: 335.2483.

*4.6.19. 1,2-Diphenyl-N-((R)-1-phenylethyl)ethylamine[23] (**8a**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3061, 3026, 2924, 2852, 1493, 1452, 1155, 1129, 1070, 1028, 758, 696. ^{1}H NMR: δ 7.33–7.30 (m, 2H), 7.29–7.27 (m, 1H), 7.27–7.24 (m, 2H), 7.24–7.22 (m, 2H), 7.22–7.19 (m, 2H), 7.19–7.17 (m, 1H), 7.15–7.11 (m, 2H), 7.10–7.07 (m, 1H), 6.92–6.88 (m, 2H), 3.83 (dd, J=8.9, 5.6 Hz, 1H), 3.76 (q, J=6.5 Hz, 1H), 3.18 (dd, J=13.2, 5.6 Hz, 1H), 2.87 (dd, J=13.2, 8.9 Hz, 1H), 1.32 (d, J=6.5 Hz, 3H). ^{13}C NMR: δ 146.4, 144.0, 140.1, 130.4, 129.6, 129.3, 129.1, 128.8, 128.2, 128.1, 127.9, 127.1, 63.7, 56.2, 44.1, 22.4. MS, m/z (relative intensity): 210 (94), 165 (9), 106 (100), 91 ([C_7H_7]$^+$, 9), 79 (38), 77 ([C_6H_5]$^+$, 21), 51 (5). HRMS calcd for $C_{22}H_{23}N$ [M+H]$^+$: 302.1909, found: 302.1916.

4.6.20. 1-Phenyl-N-((R)-1-phenylethyl)-2-(o-tolyl)ethylamine (**8b**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 3061, 3025, 2962, 2924, 2860, 1492, 1451, 1369, 1118, 1070, 1054, 1026, 844, 756. ^{1}H NMR: δ 7.33–7.26 (m, 2H), 7.26–7.23 (m, 1H), 7.23–7.21 (m, 2H), 7.21–7.19 (m, 2H), 7.19–7.16 (m, 1H), 7.11–7.07 (m, 2H), 6.99–6.96 (m, 1H), 6.91–6.89 (m, 1H), 6.89–6.87 (m, 1H), 6.79–6.75 (m, 1H), 3.83 (dd, J=9.0, 5.5 Hz, 1H), 3.78 (q, J=6.7 Hz, 1H), 3.20 (dd, J=13.3, 5.5 Hz, 1H), 2.87 (dd, J=13.3, 9.0 Hz, 1H), 2.02 (s, 3H), 1.31 (d, J=6.7 Hz, 3H). ^{13}C NMR: δ 146.6, 144.3, 138.3, 137.7, 131.4, 131.1, 129.6, 129.3, 128.7, 128.2, 128.1, 127.9, 127.3, 126.6, 62.4, 56.5, 41.6, 22.7, 19.6. MS, m/z (relative intensity): 210 ([M−C_8H_9]$^+$, 100), 165 (5), 106 (100), 79 (28), 77 ([C_6H_5]$^+$, 16). HRMS calcd for $C_{23}H_{25}N$ [M+H]$^+$: 316.2065, found: 316.2074.

4.6.21. 1-(2-Fluorophenyl)-2-phenyl-N-((R)-1-phenylethyl)ethylamine (**8c**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 3062, 3027, 2963, 2924, 1487, 1453, 1216, 1128, 1077, 1029, 824, 755, 697. ^{1}H NMR: δ 7.22–6.80 (m, 14H), 4.14 (dd, J=8.9, 5.7 Hz, 1H), 3.62 (q, J=6.6 Hz, 1H), 3.11–3.04 (m, 1H), 2.85–2.78 (m, 1H), 1.20 (d, J=6.6 Hz, 3H). ^{13}C NMR: δ 165.3 (d, J=243.2 Hz), 146.2, 139.7, 130.3, 130.1 (d, J=4.7 Hz), 129.8 (d, J=8.4 Hz), 129.5, 129.1, 128.2, 127.9, 127.7, 127.2, 125.3 (d, J=3.4 Hz), 116.1 (d, J=23.0 Hz), 56.7, 56.6, 43.0, 22.5. ^{19}F NMR: δ −123.42. MS, m/z (relative intensity): 216 ([M−C_7H_7]$^+$, 100), 153

(7), 112 (86), 105 ($[C_8H_9]^+$, 62), 103 (15), 85 (14), 79(14), 77 ($[C_6H_5]^+$, 11). HRMS calcd for $C_{22}H_{22}FN$ $[M+H]^+$: 320.1815, found: 320.1819.

4.6.22. 2-Phenyl-N-((R)-1-phenylethyl)-1-(thiophen-3-yl)ethylamine (**8d**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 3061, 3026, 2961, 2922, 2850, 1493, 1452, 1127, 1077, 1028, 780, 761, 697, 653. ^1H NMR: δ 7.24–7.18 (m, 3H), 7.17–7.11 (m, 3H), 7.05–6.96 (m, 3H), 6.88 (dd, J=5.1, 1.3 Hz, 1H), 6.82 (dd, J=2.8, 1.0 Hz, 1H), 6.82–6.77 (m, 2H), 3.97 (dd, J=9.1, 5.3 Hz, 1H), 3.82 (q, J=6.6 Hz, 1H), 3.19 (dd, J=13.1, 5.3 Hz, 1H), 2.87 (dd, J=13.1, 9.1 Hz, 1H), 1.35 (d, J=6.6 Hz, 3H). ^{13}C NMR: δ 146.2, 145.0, 140.1, 130.3, 129.6, 129.1, 128.2, 127.9, 127.5, 127.2, 126.7, 123.1, 59.1, 56.5, 43.4, 22.5. MS, *m/z* (relative intensity): 216 ($[M-C_7H_7]^+$, 100), 153 (7), 112 (86), 105 ($[C_8H_9]^+$, 62), 103 (15), 85 (14), 79 (14), 77 ($[C_6H_5]^+$, 11). HRMS calcd for $C_{20}H_{21}NS$ $[M+H]^+$: 308.1473, found: 308.1458.

4.6.23. Ethyl 3-phenyl-2-(((R)-1-phenylethyl)amino)propanoate (**8e**).* Yellow oil. FT-IR (neat, cm^{-1}): ν 3062, 3030, 2932, 1729, 1494, 1453, 1179, 1136, 1027, 759, 698. ^1H NMR: δ 7.20–7.18 (m, 1H), 7.18–7.17 (m, 2H), 7.16–7.14 (m, 2H), 7.13–7.11 (m, 1H), 7.11–7.08 (m, 2H), 7.05–7.01 (m, 2H), 3.80–3.66 (m, 2H), 3.65 (q, J=6.7 Hz, 1H), 3.36 (dd, J=8.2, 5.9 Hz, 1H), 2.94–2.88 (m, 1H), 2.80–2.73 (m, 1H), 1.21 (d, J=6.7 Hz, 3H), 0.89 (t, J=7.1 Hz, 3H). ^{13}C NMR: δ 144.3, 138.3, 137.7, 131.4, 131.1, 129.6, 129.3, 128.7, 128.2, 127.9, 127.3, 126.6, 62.6, 61.2, 57.9, 40.3, 23.3, 14.3. MS, *m/z* (relative intensity): 224 ($[M-CO_2Et]^+$, 20), 206 ($[M-C_7H_7]^+$, 53), 120 (35), 105 ($[C_8H_9]^+$, 100), 102 (25), 91 ($[C_7H_7]^+$, 42), 79 (17), 74 (5). HRMS calcd for $C_{19}H_{23}NO_2$ $[M+H]^+$: 298.1807, found: 298.1816.

4.6.24. N-((S)-1-(Naphthalen-2-yl)ethyl)-1,2-diphenylethylamine (**10**).* Colorless oil. FT-IR (neat, cm^{-1}): ν 3027, 2925, 2848, 1510, 1494, 1452, 1169, 1118, 1071, 1028, 799, 777, 757, 697. ^1H NMR: δ 7.77–7.69 (m, 2H), 7.63 (d, J=7.8 Hz, 1H), 7.45 (d, J=7.3 Hz, 1H), 7.39–7.26 (m, 3H), 7.22–7.15 (m, 6H), 7.13–7.09 (m, 2H), 6.97–6.92 (m, 2H), 4.42 (q, J=6.6 Hz, 1H), 3.99 (t, J=6.6 Hz, 1H), 2.87–3.03 (m, 2H), 1.33 (d, J=6.6 Hz, 3H). ^{13}C NMR: δ 137.8, 132.9, 130.0, 128.3, 127.8, 127.3, 127.1, 126.4, 126.2, 126.1, 125.1, 124.6, 124.5, 124.3, 122.2, 122.0, 61.0, 49.9, 43.5, 20.7. MS, *m/z* (relative intensity): 260 ($[M-C_7H_7]^+$, 81), 155 ($[C_{12}H_{11}]^+$, 100), 128 (7), 106 (18). HRMS calcd for $C_{26}H_{25}N$ $[M+H]^+$: 352.2065, found: 352.2056.

Acknowledgements

Financial support of this work by the CNRS and the University Paris-Est Créteil (Ph.D. grant) is gratefully acknowledged.

References and notes

1. For a reference book, see:*Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.
2. For recent reviews on multicomponent reactions (MCRs) and asymmetric MCRs (AMCRs), see: (a) Arndtsen, B. A. *Chem.—Eur. J.* **2009**, *15*, 302–312; (b) Isambert, N.; Lavilla, R. *Chem.—Eur. J.* **2008**, *14*, 8444–8454; (c) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693–700; (d) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (f) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634; (g) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980; (h) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144; (i) Orru, R. V. A.; De Greef, M. *Synthesis* **2003**, 1471–1499; (j) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80; (k) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111; (l) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
3. (a) Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synthesis* **2008**, 4007–4011; (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554.
4. (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070; (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 953–973; (c) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1007–1046.
5. (a) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718–3723; (b) Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539–542; (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799; (d) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586.
6. (a) Desrosier, J.-N.; Côté, A.; Charette, A. B. *Tetrahedron* **2005**, *61*, 6186–6192; (b) Côté, A.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 10864–10867; (c) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244–4247; (d) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410.
7. (a) Fan, R.; Pu, L.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* **2007**, *72*, 3149–3151; (b) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437–2440; (c) Gommermann, N.; Knochel, P. *Tetrahedron* **2005**, *61*, 11418–11426; (d) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis* **2004**, 2015–2025; (e) Bieber, L. W.; Da Silva, M. F. *Tetrahedron Lett.* **2004**, *45*, 8281–8283; (f) Estevam, I. H. S.; Bieber, L. W. *Tetrahedron Lett.* **2003**, *44*, 667–670; (g) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473–4475; (h) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585; (i) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766; (j) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534–2536; (k) Choucair, B.; Léon, H.; Miré, M.-A.; Lebreton, C.; Mosset, P. *Org. Lett.* **2000**, *2*, 1851–1853.
8. For systems employing the Petasis reaction, see: (a) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470; (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446; (c) Jiang, B.; Xu, M. *Org. Lett.* **2002**, *4*, 4077–4080; (d) Southwood, T. J.; Curry, M. C.; Hutton, C. A. *Tetrahedron* **2006**, *62*, 236–242 For systems based on the Ugi reaction, see: (e) Martquarding, D.; Hoffman, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969–1971; (f) Kunz, H.; Sager, W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 557–559; (g) Ross, G. F.; Herdtweck, E.; Ugi, I. *Tetrahedron* **2002**, *58*, 6127–6133; (h) Kunz, H.; Perengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651–652; (i) Owens, T. D.; Araldi, G.-L.; Nutt, R. F.; Semple, E. J. *Tetrahedron Lett.* **2001**, *42*, 6271–6274; (j) Gulevich, A. V.; Balenkova, E. S.; Nenajdenko, V. G. *J. Org. Chem.* **2007**, *72*, 7878–7885 For the use of Mannich and related reactions, see: (k) Loh, T.-P.; Chen, S.-L. *Org. Lett.* **2002**, *4*, 3647–3650; (l) Delaye, P.-O.; Vasse, J.-L.; Szymoniak, J. *Org. Biomol. Chem.* **2010**, *8*, 3635–3637; (m) Rondot, C.; Zhu, J. *Org. Lett.* **2005**, *7*, 1641–1644; (n) Saidi, M. R.; Azizi, N. *Tetrahedron: Asymmetry* **2003**, *14*, 389–392.
9. (a) Haurena, C.; Le Gall, E.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem.* **2010**, *75*, 2645–2650; (b) Le Gall, E.; Decompte, A.; Martens, T.; Troupel, M. *Synthesis* **2010**, 249–254; (c) Le Gall, E.; Haurena, C.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem.* **2009**, *74*, 7970–7973; (d) Sengmany, S.; Le Gall, E.; Troupel, M. *Synlett* **2008**, 1031–1035; (e) Haurena, C.; Sengmany, S.; Huguen, P.; Le Gall, E.; Martens, T.; Troupel, M. *Tetrahedron Lett.* **2008**, *49*, 7121–7123; (f) Sengmany, S.; Le Gall, E.; Le Jean, C.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron* **2007**, *63*, 3672–3681; (g) Le Gall, E.; Troupel, M.; Nedelec, J.-Y. *Tetrahedron* **2006**, *62*, 9953–9965; (h) Le Gall, E.; Troupel, M.; Nédélec, J.-Y.- *Tetrahedron Lett.* **2006**, *47*, 2497–2500.
10. A single experiment involving the use of 1-phenylethylamine had been disclosed, see Ref. 9c for details.
11. Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2005**, *46*, 2025–2028.
12. Trotter, N. S.; Brimble, M. A.; Harris, P. W. R.; Callis, D. J.; Sieg, F. *Bioorg. Med. Chem.* **2005**, *13*, 501–517.
13. Proline esters were obtained as hydrochlorides thus 3 equiv of the organozinc reagent were used.
14. Furness, M. S.; Zhang, X.; Coop, A.; Jacobson, A. E.; Rothman, R. B.; Dersch, C. M.; Xu, H.; Porreca, F.; Rice, K. C. *J. Med. Chem.* **2000**, *43*, 3193–3196.
15. Bishop, M. J.; McNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311–1314.
16. Calderon, S. N.; Coop, A. *Curr. Pharm. Des.* **2004**, *10*, 733–742.
17. (a) Siwicka, A.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Zawadzka, A.; Czarnocki, Z. *Can. J. Chem.* **2007**, *85*, 1033–1036; (b) Levinger, S.; Nair, R.; Hassner, A. *Beilstein J. Org. Chem.* **2008**, *4*, No. 32; (c) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707–9718; (d) Boga, C.; Savoia, D.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1990**, *1*, 291–294; (e) Ziółkowski, M.; Czarnocki, Z.; Leniewski, A.; Maurin, J. K. *Tetrahedron: Asymmetry* **1999**, *10*, 3371–3380; (f) Soe, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347–358; (g) Xu, D.; Prasad, K.; Repič, O.; Blacklock, T. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1445–1451; (h) de Parrodi, C. A.; Juaristi, E.; Quintero, L.; Clara-Sosa, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1075–1082.
18. For some miscellaneous examples, see: (a) Bajwa, J. S.; Slade, J.; Repič, O. *Tetrahedron Lett.* **2000**, *41*, 6025–6028; (b) Liotta, L. J.; Ganem, B. *Tetrahedron Lett.* **1989**, *30*, 4759–4762; (c) Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076–4078; (d) Marzi, M.; Misiti, D. *Tetrahedron Lett.* **1989**, *30*, 6075–6076; (e) Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209–1212; (f) Cheng, C.; Sun, J.; Xing, L.; Xu, J.; Wang, X.; Hu, Y. *J. Org. Chem.* **2009**, *74*, 5671–5674.
19. (a) Balducci, D.; Contaldi, S.; Lazzari, I.; Porzi, G. *Tetrahedron: Asymmetry* **2009**, *20*, 1398–1401; (b) Ferioli, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1181–1187.
20. Metlushka, K. E.; Kashemirov, B. A.; Zheltukhin, V. F.; Sadkova, D. N.; Büchner, B.; Hess, C.; Kataeva, O. N.; McKenna, C. E.; Alfonsov, V. A. *Chem.—Eur. J.* **2009**, *15*, 6718–6722.
21. One can envisage the possible use of e.g., 4-methoxybenzyl or 2,4-dimethoxybenzyl groups, which might be selectively removed by different pathways, for some miscellaneous examples see: (a) Lechner, R.; König, B. *Synthesis* **2010**, 1712–1718; (b) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196; (c) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297–6298; (d) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451–454

For a review on protecting groups, see: (e) Jarowicki, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4005–4037 For a leading book, see: (f) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis Wiley: New York, NY, 1999.*

22. (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031–5033; (b) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Tomatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778–7786.
23. Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2001**, 4411–4418.